UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,145	12/22/2006	Shyam S. Mohapatra	USF.T192XC1	1541

23557 7590 06/18/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
06/18/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/544,145	MOHAPATRA, SHYAM S.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,12,16,24,30-32,39,43 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12,16,24,30-32,39,43 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 1 June 2010.

Claim Status

Claims 10, 12, 16, 24, 30-32, 39, 43 and 49-51 are pending. Claims 1-9, 11, 13-15, 17-23, 25-29, 33-38 and 40-42 are cancelled. No claims were amended in the filing of 6/1/2010. Claims 49-51 are newly added. Claims 10, 12, 16, 24, 30-32, 39, 43 and 49-51 are under current examination.

Priority

This application claims benefit as a 371 of PCT/US04/04262 (filed 02/13/2004) which claims benefit of 60/319,946 (filed 02/14/2003) and claims benefit of 60/319,956 (filed 02/19/2003). The instant application has been granted the benefit date, 02/14/2003, from the application 60/319,946.

RESPONSE TO ARGUMENTS

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 12, 16, 24, 30-32 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (EP1013772, published 28 June 2000) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive. The applicant has not amended pending claims 10, 12, 16, 24, 30-32 and 43 in the response of 6/1/2010.

The applicant argues that the limitation, “wherein said nanoparticle induces production of less interleukin-6 compared to a particle comprising a complex of the

chitosan, or chitosan derivative and the polynucleotide without the lipid," is unexpected and therefore non-obvious (Remarks, filed 6/1/2010, pages 4-5). The applicant argues that the examiner has an oversimplified view of Figure 4 from the instant specification. In the last Action (filed 2/1/2010), the examiner stated:

> The examiner notes that Figure 4 of the specification show the amount of IL-6 induced by polyplexes (DNA+chitosan), lipoplexes (DNA+lipid), and lipopolyplexes (DNA+chitosan+lipid). The graph of Figure 4 shows that polyplexes induce the most IL-6, lipoplexes induce the least IL-6 and lipopolyplexes induce an amount of IL-6 between the other two formulations. Therefore, the examiner concludes that as the lipopolyplexes comprise a blend of both chitosan and lipid, it is not surprising to find that the amount of IL-6 induced falls between the other two formulations. Accordingly, it is entirely predictable that a lipopolyplex induces less IL-6 than a polyplex and more IL-6 than a lipoplex.

The applicant argues that this is a significant and unexpected result. The applicant further argues that a skilled artisan "would not have expected a decrease in IL-6 when an increase in transfection efficiency in lung epithelial cell is observed." (Remarks, page 5, 1st parag.). As has previously been discussed in the record (Action, filed 2/1/2010, page 11, discussing the teachings of Han et al. (Molecular Therapy. Oct 2000; 2(4): 302-317)), a skilled artisan would be aware that lipopolyplex nanoparticles are highly efficient transfection agents.

Furthermore, the basis of the applicant's claim to patentability seems to be the observation that known methods of gene therapy to lung epithelial using DNA-chitosan-lipopolyplex nanoparticles results in a reduced amount of IL-6 induction relative to DNA-chitosan nanoparticles lacking lipids. Furthermore, MPEP 2112 indicates "something which is old does not become patentable upon the discovery of a new property." It is the applicant's duty to show unobviousness of the limitation, "wherein said nanoparticle induces production of less interleukin-6 compared to a particle comprising a complex of

the chitosan, or chitosan derivative and the polynucleotide without the lipid." While the applicant has asserted, "[w]hen taken in the context of IL-6, a pro-inflammatory cytokine, within the respiratory epithelium, this is a significant and unexpected result" (Remarks, page 5, parag.1), the applicant has not actually demonstrated any unexpected evidence of such an allegation. Therefore, taken as a whole, the examiner concludes that the claimed method is obvious in view of Boussif, who suggests all the active method steps. The art is also aware that DNA-lipopolyplex nanoparticles are highly efficient transfection agents. Therefore, there is no basis for patentability when considering only the active method steps. The applicant's effort to gain a patent solely on the basis of an intrinsic property of known method does not seem proper to the examiner in light of MPEP 2112. Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant has pointed to MPEP 716.02(a) to promote his view that the claimed method is non-obvious (Remarks, page 5, 2nd parag.). The examiner notes that MPEP 716.02(a) is found under the sections discussing 37 CFR 1.132 Declarations. Besides the fact that the applicant has not provided an a 1.132 affidavit, MPEP 716.02(a) requires that "evidence must show unexpected results." As far as the examiner can determine from the record and specification, a "greater than expected result" has not been provided. Therefore, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 10, 12, 16, 24, 30-32 and 43 under 35 U.S.C. 103(a) as being unpatentable over Boussif et al.

The examiner reiterates the pending rejection:

Claims 10, 12, 16, 24, 30-32 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (EP1013772, published 28 June 2000).

Claim 10 is directed to a method for delivery and expression of a polynucleotide to respiratory epithelium of a mammal, said method comprising administering a nanoparticle to the respiratory epithelium, wherein the nanoparticle comprises a complex of chitosan, or a chitosan derivative, a lipid, and a polynucleotide, wherein said polynucleotide is expressed in the respiratory epithelium, wherein said nanoparticle induces production of less interleukin-6 compared to a particle comprising a complex of the chitosan, or chitosan derivative and the polynucleotide without the lipid.

Boussif et al. teach methods of gene therapy (page 15, parag.0081, lines 41-42) to respiratory epithelium (page 15, parag.0079, line 37) using nanoparticles (page 8, parag.0042) comprising lipopolyplexes (page 7, lines 37-38). Boussif et al. teach that the cationic polymer can be chitosan (page 9, parag.0051, line 45). Accordingly, Boussif et al. suggest the gene therapy method comprising delivery to respiratory epithelium by administering the lipopolyplex (i.e., DNA+chitosan+lipid) nanoparticle described in claim 10.

In previous remarks, the applicant has argued that the following limitations must be taught by the cited art: "wherein said nanoparticle induces production of less interleukin-6 compared to a particle comprising a complex of the chitosan, or chitosan derivative and the polynucleotide without the lipid." The examiner notes that Figure 4 of the specification show the amount of IL-6 induced by polyplexes (DNA+chitosan),

lipoplexes (DNA+lipid), and lipopolyplexes (DNA+chitosan+lipid). The graph of Figure 4 shows that polyplexes induce the most IL-6, lipoplexes induce the least IL-6 and lipopolyplexes induce an amount of IL-6 between the other two formulations. Therefore, the examiner concludes that as the lipopolyplexes comprise a blend of both chitosan and lipid, it is not surprising to find that the amount of IL-6 induced falls between the other two formulations. Accordingly, it is entirely predictable that a lipopolyplex induces less IL-6 than a polyplex and more IL-6 than a lipoplex.

Claim 12 is directed to the method of claim 10, wherein the polynucleotide encodes a cytokine. Boussif et al. teach administering a polynucleotide encoding various cytokines, including interferon (page 12, parag.0063, line 12).

Claim 16 is directed to the method of claim 10, wherein the nanoparticle is administered within a composition comprising a pharmaceutically acceptable carrier. Boussif et al. teach pharmaceutical compositions of the invention (page 14, parag. 71, line 33).

Claim 24 is directed to the method of claim 10, wherein the particle is administered intranasally. Boussif et al. describe intranasal administration of DNA complexes and thereby suggest such a method (page 3, parag.0030, line 33).

Claim 30 is directed to the method of claim 10, wherein said particle comprises a chitosan derivative. Boussif et al. suggest chitin derivatives (page 9, parag.0050, line 47). Furthermore, using a derivative of a component of a composition would be an obvious variant.

Claim 31 is directed to the method of claim 10 wherein the mammal is human. Boussif et al. teach treating the human body (page 14, parag.0073, line 39).

Claim 32 is directed to the method of claim 10, wherein said particle is administered to the respiratory tract of the mammal. Boussif et al. teach treating lung.

Claim 43 is directed to the method of claim 10, wherein said lipid is a cationic lipid. Boussif suggest nanoparticles comprising lipopolyplexes, wherein the lipids are cationic lipids.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to use a lipopolyplex composition of chitosan, a lipid, and a polynucleotide for delivery (and expression) of a polynucleotide to the respiratory epithelium of a mammal.

The person of ordinary skill in the art would have been motivated to use this method because Boussif et al. suggest lung gene therapy encompassing such nanoparticle lipopolyplexes. Boussif has indicated that these nanoparticles are stable and have high transfection efficiency.

An artisan would have expected success, because formulating polylipoplexes were known in the art prior to the instant application and Boussif suggests that the lipopolyplexes would be advantageous for delivering nucleic acids to respiratory epithelium.

Therefore the methods as taught by Boussif et al. would have been *prima facie* obvious over the methods of the instant application.

Boussif & Vijayanathan

Claim 39 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (EP1013772, published 28 June 2000) as applied to claim 10 above, and further in view of Vijayanathan et al. (*Biochemistry*. Dec.3, 2002, 41(48):14085-14094) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive. The applicant has not amended pending claim 39 in the response of 6/1/2010.

The applicant states: "Applicant's aforementioned remarks concerning IL-6 are incorporated herein by reference." (Remarks, page 6, line 3). In response, the examiner refers the applicant to the examiner's discussion above.

The applicant further argues that the examiner has not provided a reasonable basis for suggesting that the DNA-lipopolyplex nanoparticles form a plurality of polynucleotide-lipid inverted cylindrical micelles arranged in a hexagonal lattice (Remarks, page 6). Contrary to the applicant's assertion, the examiner has provided a reasonable basis for concluding that the limitations of claim 39 are taught by Boussif in view of Vijayanathan. The examiner included in the previous Action (filed 2/1/2010, pages 9-10) the following discussion:

> Vijayanathan et al. teach that non-viral delivery vehicles comprising polycationic lipids and cationic polymers (including chitosan) condense DNA into nanoparticles having columnar hexagonal liquid crystalline structures. Further, Vijayanathan teach that the particles mimic the cytoplasmic monolayer of the plasma membrane. Since the teachings of Vijayanathan et al. encompass nanoparticles comprising the same materials as Boussif et al. and the instant claims, the examiner concludes the arrangement of such nanoparticles into a hexagonal lattice is a natural consequence of the chemical nature of these particles.

As the applicant has provided no evidence that the nanoparticles of Boussif made of the same materials as those of the instant claims do not condensed DNA into arrangements having a hexagonal lattice. Also, it is clear (from the teachings of Vijayanathan) that the applicant is not the first artisan in the field of gene therapy to observe DNA-nanoparticles "wherein said polynucleotide is surrounded by a monolayer of lipid, and wherein said nanopoarticle comprises a plurality of polynucleotide-lipid inverted cylindrical micelles arranged in a hexagonal lattice." Vijayanathan clearly indicates that many types of DNA nanoparticles have columnar hexogonal liquid crystalline structures. The applicant has provided no scientific basis for a skilled artisan to believe that the claimed nanoparticles would not form such hexagonal lattices. Therefore, the applicant's argument is not persuasive.

Therefore, the examiner hereby maintains the rejection of claim 39 under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. as applied to claim 10 above, and further in view of Vijayanathan et al.

The examiner reiterates the pending rejection:

Claim 39 rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (EP1013772, published 28 June 2000) as applied to claim 10 above, and further in view of Vijayanathan et al. (*Biochemistry*. Dec.3, 2002, 41(48):14085-14094)..

The teachings of Boussif are recited above in the previous 35 USC 103 rejection.

Boussif fails to teach the limitations of claim 39, directed to "wherein said polynucleotide is surrounded by a monolayer of lipid, and wherein said nanopoarticle

comprises a plurality of polynucleotide-lipid inverted cylindrical micelles arranged in a hexagonal lattice."

Vijayanathan et al. teach that non-viral delivery vehicles comprising polycationic lipids and cationic polymers (including chitosan) condense DNA into nanoparticles having columnar hexagonal liquid crystalline structures. Further, Vijayanathan teach that the particles mimic the cytoplasmic monolayer of the plasma membrane. Since the teachings of Vijayanathan et al. encompass nanoparticles comprising the same materials as Boussif et al. and the instant claims, the examiner concludes the arrangement of such nanoparticles into a hexagonal lattice is a natural consequence of the chemical nature of these particles.

No rationale for obviousness is required since Vijayanathan demonstrates the limitations of claim 39 are an intrinsic characteristic of the nanoparticles described. The limitations of claim 39 do not provide additionally active steps which further limit the claimed method. Accordingly, the limitations of claim 39 are obvious.

Furthermore, MPEP 2112 indicates "something which is old does not become patentable upon the discovery of a new property." It is the applicant's duty to show unobviousness of the limitation of claim 39.

Therefore the methods as taught by Boussif et al. and Vijayanathan et al. would have been *prima facie* obvious over the methods of the instant application.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Boussif & Dow

Claims 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (EP1013772, published 28 June 2000) as applied to claim 10 and 12 above, and further in view of Dow et al. (Human Gene Therapy. 1999; 10:1905-1914).

The teachings of Boussif et al. are recited above in a previous 35 USC § 103 section.

While Boussif et al. teach delivery and expressing of a polynucleotide interferon complexes with chitosan and a lipid, Boussif et al does not teach administration of the particular cytokine, interferon-gamma (claim 49). While Boussif suggests a gene therapy method for respiratory epithelium, Boussif does not particularly suggest treating asthma (50-51).

Dow et al teach interferon-γ gene delivery to the lungs for treatment of asthma (abstract). Dow et al. further teach using lipid-DNA complexes.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to use the generic methodology of Boussif for the particular utility of interferon-γ gene delivery to the lungs for treatment of asthma (as taught by Dow).

The person of ordinary skill in the art would have been motivated to combine the teachings of Boussif and Dow, because Boussif et al. suggest that their method can be used for delivery of therapeutic molecules in individuals having needs of such treatment, whereas Dow et al. teach individuals with asthma have need of interferon-γ gene

delivery to the lungs. Furthermore, Dow et al. indicate that gene therapeutic method of delivering interferon-gamma was more effective that recombinant interferon-gamma.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (delivery of interferon DNA-lipopolyplexes to respiratory epithelium, and IFN-γ gene therapy for asthma) are taught by Boussif or Dow. It would be therefore predictably obvious to use a combination of these elements in a method for delivery and expression in respiratory epithelium of a mammal.

An artisan would have expected success, because Dow indicates that DNA-lipid complexes are successful for inducing interferon-gamma expression in respiratory epithelium and producing a therapeutic response, whereas Boussif teach that interferon DNA-lipopolyplexes can be successfully delivered to respiratory epithelium.

Therefore the method as taught by Boussif et al. in view of Dow et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633